The effect of furosemide on intracranial pressure and hemorrhage in preterm rabbits

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The hypothesis that intracranial hypotension due to excessive postnatal fluid loss places the premature infant at risk for germinal matrix and intraventricular hemorrhage (GM-IVH) was tested in preterm rabbits delivered at 28 and 29 days of gestation (term 32 days). Furosemide administered to newborn pups induced a diuresis that resulted in a 11% to 22% loss in body weight and a concomitant decline in muscle water (13% to 16%) and sodium (18% to 21%). Paradoxically, no change occurred in the water or electrolyte content of the brain even though cerebrospinal fluid and brain tissue pressure, but not blood pressure, declined. These changes were absent in littermates treated with saline. Microscopic examination of brain sections revealed a greater incidence of intracranial hemorrhage, particularly in the germinal matrix and choroid plexus, in furosemide-treated than in saline-treated preterm rabbit pups. These results are consistent with the hypothesis that intracranial hypotension promotes the incidence of GH-IVH in preterm animals.

Key Words: furosemide • intracranial pressure • intraventricular hemorrhage • germinal matrix hemorrhage • preterm rabbits

GERMINAL matrix and intraventricular hemorrhage (GM-IVH) is recognized as one of the more serious complications of premature birth. 35,48 This disorder is estimated to occur in 40% to 60% of premature infants weighing 1500 gm or less at birth 3,5,6,36 and to cause the death of 0.1% of all babies born alive. Those who survive the immediate effects of this postnatal disorder may develop seizures, sensorimotor deficits, intellectual impairment, or hydrocephalus. 2,25,57

The germinal matrix is the most prominent site of hemorrhage, 21,26 but other sites of origin are recognized. 20,34,42 Although numerous factors have been implicated in the pathogenesis of GM-IVH, 15,17,18,44 the etiology remains obscure. The object of this study was to investigate the role that intracranial hypotension may play in the pathogenesis of these hemorrhages. In previous studies it was shown that the administration of hyperosmotic solutions of glycerol to preterm rabbits lowered intracranial pressure (ICP) and coincidentally increased the incidence of GM-IVH fourfold. 7 However, this was associated with a significant increase in plasma osmolality. In the present study, furosemide administration was found to be effective in lowering ICP and increasing the incidence of GM-IVH in preterm rabbits without altering plasma osmolality.

Materials and Methods

Animal Groups

This study was carried out in compliance with the National Institutes of Health "Guide for the Care and Use of Laboratory Animals" and was further approved by the Children's Hospital Animal Review Committee. New Zealand White rabbit fetuses were delivered by Caesarean section at 28 or 29 days of gestation as described in previous reports. 7,28,30 One group of 16 animals (from seven litters) was used to monitor cerebrospinal fluid (CSF) and brain tissue pressure. A second group containing eight animals (from three litters) underwent ventriculocisternal perfusion 29 to determine the effect of furosemide on CSF formation. The third group consisting of 65 preterm pups (from 17 litters) was used to assess tissue water and electrolyte content as well as the incidence and locus of intracranial hemorrhage following saline treatment (control group) or furosemide treatment. Except for the brief period required to make the intraperitoneal injection of furose-
mide or an equal volume of saline, these animals remained unmolested in their nest until they were killed. Preterm pups in the first two groups were not used to assess the overall incidence of GM-IVH since the manipulation associated with the surgical procedures could affect the incidence of intracranial hemorrhage.

**CSF and Brain Tissue Pressures**

The procedures used to monitor CSF and brain tissue pressure have been described in detail in previous reports from this laboratory. Briefly, preterm rabbit pups were anesthetized with tribromoethanol (90 to 125 mg/kg intraperitoneally) supplemented with lidocaine (0.5%) injected locally into all incision and pressure point sites. The trachea was cannulated and polyethylene (PE 10) catheters filled with heparinized saline (100 USP units/ml) were inserted into the femoral artery and vein. The animal was then placed in a sphincter-like position with its head held in a stereotaxic frame modified for small animals. * Body temperature was maintained at 37.5°C with a thermostatically controlled heating blanket connected to a thermistor probe inserted into the rectum.

A midline incision was made in the scalp, the skin was reflected, and the underlying cranium was exposed. A hole, located 1 to 1.5 mm caudal to the coronal suture and 2 mm lateral to the sagittal suture, was made through the temporal bone with a 1-mm burr held in an electric dental drill. The external bone landmarks, rather than the interaural line, were used as the zero reference point since no stereotaxic atlases exist for rabbits of this age.

Fluid-filled cannulas, made from short beveled No. 23 thin-walled needles connected distally with semi-rigid Teflon tubing to three-way microvalves attached directly to pressure transducers, were used to monitor CSF and brain tissue pressure.† Compliance of these systems, determined by infusing fluid at a constant rate of 0.24 ml/min into the system with the cannula tip occluded, ranged from 0.50 ± 0.13 × 10⁻⁵ to 1.2 ± 0.19 × 10⁻⁵ ml/mm Hg (± standard deviation). Baseline drift, evaluated over a 4-hour period, was less than 1.5 mm H₂O/hr.

One of the cannulas was inserted percutaneously into the cisterna magna and the other was advanced stereotaxically through the burr hole into the underlying cortex. Correct placement of the cannula in the cisterna magna was indicated by the appearance of cardiac and respiratory pulsations in the recording. Infusion of fluid at a rate of 0.2 µl/min into the brain tissue-pressure cannula for 1 to 2 seconds normally resulted in a rapid and sustained increase in brain tissue pressure when the tip of the cannula lay within the parenchyma and did not communicate with the subarachnoid or ventricular spaces. Dental cement was used to seal the hole around the brain tissue cannula. The pressure transducers were placed 4 to 5 cm below the level of the manubrium sterni, which was used as the zero reference point for all pressure calibrations. The transducer signals were amplified and continuously recorded on a polygraph.‡ After calibration, a 60- to 90-minute recording was made of the various pressures, and a single parenteral dose of furosemide (10, 20, or 50 mg/kg) was administered. Recordings were continued for an additional 1 to 2 hours. Arterial blood samples (0.2 ml) were drawn at various intervals during the recording sessions for determination of blood pH and gases. The animals were killed with an intravenous overdose of pentobarbital (50 mg/kg) and the brains were promptly removed, placed in buffered formalin, and subsequently processed for histological and microscopic examination. Sections 10 µ thick, stained with hematoxylin and eosin (H & E), were examined to confirm the locus and extent of penetration of the brain tissue cannula.

**Ventriculocisternal Perfusion**

This group of animals was treated in the same manner as above except that the brain tissue cannula was advanced into the lateral ventricle. Ventriculocisternal perfusions were made with rabbit artificial CSF¹¹ using a modification ²⁹,³⁸ of the method first described by Adam, et al.¹ Briefly, the artificial CSF, which contained iodine-125-labeled human serum albumin (¹²⁵I-HSA) as a nondiffusible indicator of CSF formation, was introduced at a constant rate of 100 µl/min through the ventricular needle and was collected from the distal orifice of the Teflon tubing connected to the cisternal needle. The outflow was collected in 20-drop fractions which were counted in a scintillation gamma counter at 50% efficiency.§ A steady state was indicated when the activity in at least three consecutive tubes remained constant. Formation of CSF (Vᵢ) was calculated using the equation introduced by Heisey, et al., ²² where Vᵢ represents the inflow rate (ml/min), and Cᵢ and Cₒ, are the concentrations of ¹²⁵I-HSA (dpm/ml) in the inflow and outflow, respectively:

\[
Vᵢ = Vᵢ \left[ \frac{Cᵢ - Cₒ}{Cₒ} \right]
\]

The first steady state was usually reached within 30 to 45 minutes after the start of the infusion, at which time a 0.5-ml blood sample was taken for determination of blood gases and pH. Three to five more tubes were collected before furosemide (50 mg/kg) was injected intravenously. The perfusion was continued for another 60 to 90 minutes, at the end of which another blood sample was taken for calculation of blood gases and pH. The animal was then killed with an overdose of

* Stereotaxic apparatus manufactured by Trent Wells, Tu- junga, California.
† Microvalves manufactured by Hamilton Co., Reno, Ne- vada; Statham P23dB pressure transducer manufactured by Gould Inc., Oxnard, California.
‡ Polygraph, Model PD-7, manufactured by Grass Instru- ment Co., Quincy, Massachusetts.
§ Scintillation gamma counter manufactured by Packard Instruments, Downers Grove, Illinois.
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### TABLE 1

<table>
<thead>
<tr>
<th>Factor</th>
<th>Gest. Age: 28 Days + 1</th>
<th>Gest. Age: 29 Days + 1</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Control Group</td>
<td>Furosemide Group</td>
</tr>
<tr>
<td>no. of pups</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>no. of litters</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>body weight (gm)</td>
<td>38.6 ± 4.1</td>
<td>36.6 ± 4.4</td>
</tr>
<tr>
<td>6 hrs postinfusion</td>
<td>37.7 ± 3.9</td>
<td>32.7 ± 4.4</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>(≤ 0.05)</td>
</tr>
<tr>
<td>brain weight (gm) at 1.04 • 0.13</td>
<td>1.04 ± 0.13</td>
<td>1.07 ± 0.08</td>
</tr>
<tr>
<td>6 hrs postinfusion</td>
<td>307 ± 9</td>
<td>306 ± 11</td>
</tr>
<tr>
<td>osmolality (mOsm)</td>
<td>48 ± 3</td>
<td>51 ± 3</td>
</tr>
<tr>
<td>hematocrit (%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Values are means ± standard deviation. Gest. = gestational; NS = not significant.

Tissue Water and Electrolyte Content

Animals in the third group were injected intraperitoneally with furosemide (50 mg/kg) or an equal volume of saline (control group) before being returned to their nest. Six hours later, the pups were anesthetized with tribromoethanol (90 mg/kg intraperitoneally), and 1.5 to 2.5 ml of blood was drawn from the heart via direct cardiac puncture. Duplicate aliquots were used to determine hematocrit (0.1 ml) and osmolality (0.2 ml) by freezing-point depression. The brains were then removed and weighed, and as quickly as possible the frontal poles (cortex) were separated and placed in tared weighing flasks and weighed. Tissue water content was determined following desiccation of tissues to a constant weight in a vacuum oven kept at 95°C. Tissue water content per gram dry weight (dw) was calculated as follows:

\[
\text{water content}_{(dw)} = \frac{\text{tissue wet weight (gm)} - \text{tissue dry weight (gm)}}{\text{tissue dry weight (gm)}}
\]

The desiccated tissue was then removed from the vials and digested in 20% HNO₃ containing 15 mEq of LiNO₃. Sodium and K⁺ concentrations in plasma and in aliquots of the tissue digests were determined by means of flame photometry.*

Microscopic Assessment of Intracranial Hemorrhage

The remainder of the brain was placed in 10% buffered formalin; after fixation, coronal blocks 3 to 5 mm thick were cut by hand with a stainless steel blade. The blocks were dehydrated in ascending concentrations of alcohol, cleared, and embedded in paraffin. A rotary microtome was used to cut six to eight coronal sections 10 μm thick from each paraffin block. The sections, which were stained with H & E and coded to prevent observer bias, were examined independently by two of the investigators (A.V.L. and G.W.H.) by light microscopy. Hemorrhages occurring at any particular brain site had to appear in at least two consecutive sections to be counted.

Results

Effect on Body and Brain Weight

As shown in Table 1, preterm pups randomly assigned to a control group and the experimental group had comparable body weights at birth. Pups treated with saline maintained their weight during the 6-hour experimental period; however, littermates treated with furosemide lost 11% (28 days gestation) to 22% (29 days gestation) of their body weight during the same interval. It is of interest that the average brain weights of the control and furosemide-treated pups were similar, indicating that the diuretic agent did not affect brain water content. Furosemide also did not affect plasma osmolality or electrolyte content (see Table 4), but did cause a significant increase in the hematocrit.

Effect on CSF and Brain Tissue Pressures

In brain tissue pressure recordings, cardiac and respiratory fluctuations were minimal or not discernible (Fig. 1). Normally, CSF pressure was higher than brain tissue pressure (Table 2), and following the administration of furosemide both CSF and brain tissue pressures fell promptly (Fig. 2 and Table 2).

Effect on CSF Formation

Table 3 shows that CSF formation which averaged 5.7 ± 1.2 μl/min during the control period was reduced by 48% following furosemide administration. No sig-
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FIG. 1. Polygraphic pressure recordings of brain tissue (TISS P), cisterna magna (CSF P), and femoral artery (ART P) from a preterm rabbit delivered at 29 days of gestation. Arrow indicates intravenous furosemide administration (50 mg/kg). EKG = electrocardiographic recording.

Significant changes were observed in the blood pH, pCO2, or pO2 after furosemide administration.

Effect on Tissue Water and Electrolyte Content

Brain water content and electrolyte concentration in furosemide-treated pups were similar to those of saline-treated littermates (Table 4). However, in muscle, furosemide caused a significant decrease in water (13% to 16%) and Na+ (18% to 21%) content, and an increase in K+ (10%).

**TABLE 2**

**Effect of furosemide on CSF and brain tissue pressure of preterm rabbits***

<table>
<thead>
<tr>
<th>Factor</th>
<th>Pre-Furosemide</th>
<th>Post-Furosemide</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of pups</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>no. of litters</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>body weight (gm)</td>
<td>41.8 ± 11.3</td>
<td>36.2 ± 8.7</td>
</tr>
<tr>
<td>arterial pressure (mm Hg)</td>
<td>29 ± 9</td>
<td>31 ± 10</td>
</tr>
<tr>
<td>CSF pressure (cm H2O)</td>
<td>2.8 ± 1.6</td>
<td>0.9 ± 1.3</td>
</tr>
<tr>
<td>brain tissue pressure (cm H2O)</td>
<td>2.3 ± 1.4</td>
<td>1.0 ± 1.1</td>
</tr>
</tbody>
</table>

* Combined results from preterm rabbits pups delivered on Day 28 or 29 of gestation. CSF = cerebrospinal fluid. Values are means ± standard deviation.

Effect on Incidence of Intracranial Hemorrhage

Hemorrhages in the germinal matrix (GMH) overlying the head of the caudate nucleus (Fig. 3A) appeared as either diffuse (Fig. 3B) or consolidated (Fig. 3C). In some instances, these hemorrhages caused the ependyma to bulge into the lateral ventricle and clumps of free erythrocytes could be seen within the ventricular cavities. Some of the animals with GMH also had hemorrhages in the choroid plexus lying within the body of the lateral ventricles (Fig. 3D) as well as within the third ventricle. In such cases, groups of erythrocytes could be observed floating freely within or lining the ependymal walls of the ventral recesses of the lateral and third ventricles, and within the aqueduct. However, the amount of blood within the ventricular cavities was never sufficient to cause dilatation of the ventricle.

Table 5 shows that preterm rabbits given furosemide had a higher incidence of intracranial hemorrhage than saline-treated littermates. Parenchymal GMH, where the incidence was greatest (control group 28%, furosemide group 68%), were mostly represented by small consolidated hemorrhages (Fig. 3C), although some hemorrhages were diffuse (Fig. 3B). Bleeding from the choroid plexus was also prominent, with groups of erythrocytes appearing to be floating free and/or adhering to the walls of the lateral, third, or fourth ventricles.

**TABLE 3**

**Effect of furosemide on CSF formation and blood pH and gases***

<table>
<thead>
<tr>
<th>Factor</th>
<th>Pre-Furosemide</th>
<th>Post-Furosemide</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of pups</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>no. of litters</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>CSF formation (μl/min)</td>
<td>5.7 ± 1.2</td>
<td>3.0 ± 1.1</td>
</tr>
<tr>
<td>blood pH</td>
<td>7.35 ± 0.05</td>
<td>7.37 ± 0.08</td>
</tr>
<tr>
<td>blood pCO2 (mm Hg)</td>
<td>31.9 ± 9.1</td>
<td>26.4 ± 7.8</td>
</tr>
<tr>
<td>blood pO2 (mm Hg)</td>
<td>67.6 ± 12.5</td>
<td>78.3 ± 13.4</td>
</tr>
</tbody>
</table>

* Combined results from 3- to 5-day-old preterm rabbit pups delivered on Day 28 or 29 of gestation. CSF = cerebrospinal fluid. Values are means ± standard deviation.
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In some animals, free erythrocytes could be detected within the aqueduct. An increase in hemorrhages was also detected in other areas of the brain such as the cerebral cortex (control group 14%, furosemide group 37%), subcortical white matter (control group 14%, furosemide group 32%), and septal nuclei (control group 14%, furosemide group 37%).

Discussion

The effectiveness of furosemide in lowering elevated ICP induced by either head trauma or cold-induced edema has been attributed to the ability of the diuretic agent to lower brain water content. However, others have failed to observe a reduction in brain water and electrolyte content following furosemide administration. In the present study, furosemide was observed to cause a marked decrease in body weight, as well as in the water and Na⁺ content of muscle—changes which can reasonably be attributed to secondary effects of the diuretic. Even though the concentration of furosemide used has been shown to lower CSF and brain tissue pressure, and to reduce the water and Na⁺ content of muscle of newborn preterm rabbits, no changes were observed in the water and electrolyte content of the brain of these animals. This inability of furosemide to affect brain water content is consistent with the work of Davson and Segal who showed that acetazolamide, another diuretic agent which also acts

![FIG. 3. Coronal brain sections from preterm rabbits. H & E. A: Germinal matrix (arrows) at the level of the head of the caudate nucleus (cn) and lateral ventricle (V). x 18.5. B: Germinal matrix hemorrhage (filled arrows) bordering the head of the caudate nucleus. Open arrows indicate the germinal matrix. x 52. C: Germinal matrix hemorrhage (arrows) bordering the white matter. x 148. D: Choroid plexus (cp) hemorrhage in the lateral ventricle. Erythrocytes oozing from the choroid plexus are floating freely in the cerebrospinal fluid and lining the ependymal walls (arrows) of the ventricles. x 44.](image)

### TABLE 4

Effect of furosemide on brain and muscle tissue water and electrolytes

<table>
<thead>
<tr>
<th>Factor†</th>
<th>Gest. Age: 28 Days + 1</th>
<th>Gest. Age: 29 Days + 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control Group</td>
<td>Furosemide Group</td>
</tr>
<tr>
<td>no. of pups</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>no. of litters</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>brain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H₂O (ml/gm)</td>
<td>7.8 ± 0.4</td>
<td>7.6 ± 0.6</td>
</tr>
<tr>
<td>Na⁺ (mM/kg)</td>
<td>619 ± 46</td>
<td>642 ± 93</td>
</tr>
<tr>
<td>K⁺ (mM/kg)</td>
<td>674 ± 47</td>
<td>610 ± 69</td>
</tr>
<tr>
<td>muscle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H₂O (ml/gm)</td>
<td>7.0 ± 0.3</td>
<td>6.1 ± 0.4</td>
</tr>
<tr>
<td>Na⁺ (mM/kg)</td>
<td>712 ± 45</td>
<td>583 ± 50</td>
</tr>
<tr>
<td>K⁺ (mM/kg)</td>
<td>467 ± 35</td>
<td>480 ± 62</td>
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<tr>
<td>plasma</td>
<td></td>
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<tr>
<td>Na⁺ (mM/kg)</td>
<td>136 ± 10</td>
<td>136 ± 10</td>
</tr>
<tr>
<td>K⁺ (mM/kg)</td>
<td>5 ± 1</td>
<td>5 ± 1</td>
</tr>
</tbody>
</table>

* Values are means ± standard deviation. Gest. = gestational; NS = not significant.
† Measurements are based on dry weight.
by inhibiting carbonic anhydrase, does not affect the water content of the brain. These results suggest that the ability of furosemide to lower normal ICP in the newborn animal is not attributable to the diuretic action of the drug.

Furosemide is also known to decrease CSF formation in adult rabbits and, as indicated by the results of the ventriculocisternal perfusion studies, has a similar effect in the newborn rabbit. Presumably, this action is due to the inhibition of carbonic anhydrase in the choroid plexus, and is not secondary to the renal action of the diuretic agent. Evidence supporting this suggestion includes the ability of furosemide to reduce CSF production in nephrectomized rabbits. Whether the observed decrease in ICP can be attributed solely to inhibition of CSF formation is not clear since the ICP-volume relationship, which involves at least three compartments (vascular, interstitial, and CSF), is rather complex. Fluid or volume shifts in any one compartment may not be reflected by changes in ICP because of compensatory shifts in one of the other two compartments. Nevertheless, the time course for the decrease in ICP following acetazolamide administration to cats and rabbits has been shown to parallel the reduction in CSF outflow from the cisterna magna. Decreases in CSF pressure following the intravenous administration of acetazolamide have also been noted in cats and monkeys, but the decline in these was preceded by an increase in CSF pressure. This increase is observed following rapid intravenous injection of the drug, and not when it is infused gradually or given orally. Apparently, when the concentration of acetazolamide in blood is rapidly elevated there is a prompt inhibition of erythrocyte carbonic anhydrase. Consequently, there is an elevation in blood CO₂ which results in dilatation of cerebral blood vessels and an increase in ICP. Even though in this study furosemide was administered intravenously to the newborn rabbit pups, increases in ICP or in blood CO₂ tension could not be detected during the 6-hour experimental period (Tables 2 and 4). These results indicate that the reduction in CSF formation and ICP in our animals was most likely due to inhibition of choroid plexus carbonic anhydrase and reduction in CSF formation. It is recognized, however, that other mechanisms may be involved, since inhibition of CSF production by furosemide in rabbits can be further augmented by the subsequent administration of acetazolamide, and pretreatment of rabbits with indomethacin (a prostaglandin synthesis inhibitor) can reduce the diuretic effects of furosemide by more than 80%.

The greater incidence of intracranial hemorrhages, particularly in the germinal matrix, in furosemide-treated than in saline-treated preterm pups (Table 5) lends further support to the hypothesis that intracranial hypotension contributes to the induction of GM-IVH in preterm animals. Unlike glycerol, did not significantly alter plasma osmolality or brain water content further supports the central role that intracranial hypotension may play in the genesis of these hemorrhages. It is of interest in this respect that the incidence of choroid plexus hemorrhages was greater in this study (52%) than in our previous study (29%) in which preterm rabbit pups were treated with hyperosmotic solutions of glycerol. This could be due to a direct action of furosemide on choroid plexus blood flow (as has been reported for dogs in which furosemide is said to increase renal blood flow and to inhibit its autoregulation) or it may be secondary to the lowering of CSF pressure caused by inhibition of CSF production. Most of the hemorrhages examined were small and largely restricted to the area in which they occurred. Some of the subependymal GMH did appear to rupture the ependyma, but the amount of blood invading the ventricles was unimpressive. The low incidence of large hemorrhages, which might be classified as Grade 3 or 4 according to Papile, et al., could be attributable to the fact that the animals were killed within a relatively short period of time (6 hours after furosemide or saline injection), and there was not enough time for extension of hemorrhages. However, since preterm rabbit pups killed 6 hours after treatment with hyperosmolar solutions of glycerol had a high incidence of massive GM-IVH it is also likely that the magnitude of the pressure differential between the vascular and extravascular compartments (that is, the pressure exerted on the blood vessel wall) was greater in glycerol- than in furosemide-treated pups. In glycerol-treated pups, ICP usually fell below atmospheric or zero pressure, whereas in those treated with furosemide it rarely fell to such levels (Fig. 2).

The results of this study support the hypothesis that the differential pressure across the walls of cerebral blood vessels represents the driving force which ultimately leads to rupture of "weak" blood vessels within the germinal matrix. Postnatal events, such as intracranial hypotension, tend to magnify the pressure differential across the wall of the cerebral blood vessels.

TABLE 5

<table>
<thead>
<tr>
<th>Site of Hemorrhage</th>
<th>Control Group</th>
<th>Furosemide Group</th>
<th>p Value</th>
</tr>
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<tbody>
<tr>
<td>no. of pups</td>
<td>14</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>subarachnoid</td>
<td>4</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>cerebral cortex</td>
<td>2</td>
<td>7</td>
<td>≤ 0.05</td>
</tr>
<tr>
<td>white matter</td>
<td>2</td>
<td>6</td>
<td>≤ 0.05</td>
</tr>
<tr>
<td>germinal matrix</td>
<td>4</td>
<td>13</td>
<td>≤ 0.05</td>
</tr>
<tr>
<td>caudate nucleus</td>
<td>1</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>choroid plexus</td>
<td>0</td>
<td>10</td>
<td>≤ 0.05</td>
</tr>
<tr>
<td>ventricles lateral</td>
<td>1</td>
<td>11</td>
<td>≤ 0.05</td>
</tr>
<tr>
<td>third</td>
<td>4</td>
<td>8</td>
<td>≤ 0.05</td>
</tr>
<tr>
<td>septal nuclei</td>
<td>2</td>
<td>7</td>
<td>≤ 0.05</td>
</tr>
<tr>
<td>cerebellum</td>
<td>0</td>
<td>2</td>
<td>≤ 0.05</td>
</tr>
</tbody>
</table>

* Preterm pups in the control and furosemide groups represent littersmates selected from six litters delivered at 28 days of gestation. Values are numbers of animals. NS = not significant.

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and as a consequence place the premature newborn at risk for GM-IVH.

References


J. Neurosurg. / Volume 70 / May, 1989

Manuscript received July 27, 1988.
This work was supported in part by National Institutes of Health Grant HD-15304, Mental Retardation Center Grant P30-HD18655 from the National Institute of Child Health and Human Development, and the Vallely Family Fund.
This work was presented in part by Dr. Greene at the 29th Annual Meeting of the Society for Research Into Hydrocephalus and Spina Bifida in Manchester, England, July 3–6, 1985.
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